12. (New) The method of claim 10, wherein said composition is prepared using a purification method comprising the steps of:

(a) adjusting plasma to a pH of about 6.5 and a conductivity of between 3.5 to 6 millisiemens;

(b) contacting the plasma obtained from step (a) with an anion exchange resin to obtain an anion exchange effluent; and

(c) contacting the effluent of step (b) with a cation exchange resin to obtain a cation exchange effluent that comprises IgG4 essentially free of other IgG subtypes.

13. (New) A pharmaceutical composition, said pharmaceutical composition comprising IgG4 essentially free of other IgG subtypes and a monosaccharide or a disaccharide.

REMARKS

Claims 1-4 were pending in this application. Claims 2-4 have been canceled in this amendment without prejudice to subsequent revival of the canceled subject matter.

Claim 1 has been amended and does not add new matter. Support for the amendment to claim 1 can be found in the specification on page 5, line 20 bridging to page 9, line 3.

Claims 5-13 have been newly added. These claims are fully supported by the specification as filed and no new matter has been added. For example, support for claim 5 can be found on page 2, lines 3-7; claim 6 on page 7, line 9; claim 7 on page 7, line 19; claims 8-9 and 12 on page 5, line 20, bridging to page 9, line 3, and claims 10-11, 13 on page 1, line 1 bridging to page 2, line 21. Claims 1, 5-13 are therefore pending and subject to examination.

A version of the claims with markings to show changes to the amended claims are provided in Appendix A. All of the pending claims are provided in Appendix B for the Examiner's convenience. Reconsideration is respectfully requested.

I. THE INVENTION

The present invention relates to methods for isolating IgG4 that is essentially free of other IgG subtypes. In addition, the present invention involves methods of treating patients that have been envenomated, with compositions comprising IgG4 that is essentially free of other IgG subtypes.

II. REJECTIONS UNDER 35 U.S.C. §112, 2nd ¶

The Examiner rejected claims 1, 3, and 4 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention on several different bases. Each rejection will be treated in turn.

A. "filtering the thawed concentrated immunoglobulin solution"

Claim 1 was rejected for allegedly lacking a sufficient antecedent basis for the phrase "filtering the thawed concentrated immunoglobulin solution."

Applicant has amended claim 1 to delete the phrase "filtering the thawed concentrated immunoglobulin solution." Accordingly, Applicant respectfully requests that the rejection be withdrawn.

B. "adding sodium chloride to raw immune globulin solution to a final molarity in the range of 0.03 to 0.05 M."

The Examiner rejected claim 3 for the recitation of the phrase"adding sodium chloride to raw immune globulin solution to a final molarity in the range of 0.03 to 0.05 M." This phrase allegedly was unclear as to whether the final molarity was of sodium chloride or the raw immunoglobulin solution.

Applicant has deleted this phrase from claim 1. Claim 8 does recite "adding NaCl to a final concentration of 0.03 to 0.05 M NaCl." Clearly, this phrase provides sufficient clarity that the term "final molarity" refers to the NaCl in the solution for that step. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

C. "lyophilizing the concentrated immunoglobulin solution"

The Examiner rejected claim 3 as lacking a sufficient antecedent basis for the phrase "lyophilizing the concentrated immunoglobulin solution."

Applicant has canceled claim 3, thereby rendering this rejection moot. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

D. "purified donor plasma pool"

Claims 3 and 4 were further rejected as the phrase "purified donor plasma pool" as allegedly was indefinite.

Applicant has canceled claims 3 and 4, thereby rendering these rejections moot. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

III. REJECTION UNDER 35 U.S.C. §103(a)

Claims 1-4 were also rejected as allegedly being obvious over U.S. Patent No. 4,597,966 (the Zolton *et al.* patent), in view of U.S. Patent No. 4,186,192 (the Lundblad *et al.* patent), and further in view of *Antibodies A Laboratory Manual* by Harlow and Lane.

Applicant respectfully disagree with the Examiner's rejection. As set forth in M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. *First*, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)." As the Federal Circuit has also stated, "[a] general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel,* 34 U.S.P.Q.2d 1210, 1216 (Fed. Cir. 1995).

In the instant case, there is no motivation to modify the teaching of U.S. Patent No. 4,597,966 (the Zolton *et al.* patent), in view of U.S. Patent No. 4,186,192 (the Lundblad *et al.* patent), further in view of *Antibodies A Laboratory Manual* by Harlow and Lane to arrive at the present invention. The present invention provides the surprising discovery of methods for preparing compositions that comprise IgG4 that is essentially free of other IgG subtypes. These methods involve the use of anion exchange resins and cation exchange resins that result in the IgG4 compositions. The cited references, however, fail to provide the requisite motivation or suggestion to be combined in a manner that would arrive at the claimed invention. Therefore, Applicant respectfully maintains that the claimed invention is not obvious in light of the cited references.

There is not suggestion or motivation to modify the cited references to arrive at the present invention.

Zolton *et al.* do not contain a suggestion or motivation to make the claimed invention. The Examiner has not pointed to a *specific* motivation or suggestion to modify the purification methods disclosed in Zolton *et al.* to arrive at the claimed invention.

Zolton *et al.* disclose methods for purifying immunoglobulins that use centrifugation, followed by ultrafiltration against an imidazole solution, QAE-Sephadex chromatography (anion exchange chromatography), ultrafiltration, dialysis against a histidine

solution, filtration and vialing (see col. 6, line 54, bridging to col. 8, line 35). Zolton *et al.*, however, fail to suggest or provide a *specific* motivation to, for example, add a cation exchange step after the anion exchange chromatography step as set out in claim 1, as amended, of the present invention. Therefore, Zolton *et al.* fail to provide the requisite motivation or suggestion to modify the cited references to arrive at the claimed invention.

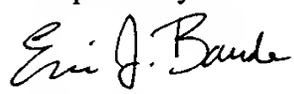
Similarly, Lundblad *et al.*, do not provide the requisite motivation or suggestion to modify the cited references. Lundblad *et al.* disclose the use of maltose and other carbohydrates to stabilize immune globulin preparations. However, Lundblad *et al.* fail to suggest or provide a motivation to use anion or cation exchange resins to manufacture a composition comprising IgG4 essentially free of other IgG subtypes. Accordingly, Lundblad *et al.* do not provide a suggestion or motivation to modify Zolton *et al.*, Lundblad *et al.* or Harlow and Lane. For example, the addition of the step of adding maltose to an immune globulin purified using the method of Zolton *et al.* (see col. 6, line 54, bridging to col. 8, line 35) would not result in the claimed invention. Such a method would not possess a cation ion exchange step following an anion exchange step.

Harlow and Lane also fail to provide the necessary suggestion or motivation to modify the cited references to arrive at the claimed invention. Harlow *et al.* disclose that antibodies should be stored at concentrations at or exceeding 1 mg/ml; Harlow *et al.* disclose that antibody preparations falling below 1 mg/ml should be concentrated prior to freezing. However, Harlow *et al.* do not provide a suggestion or motivation to, for example, to add a cation exchange step after an anion exchange step to arrive at a method that results in a composition comprising IgG4 essentially free of other IgG subtypes. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant believes all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 415-576-0200.

Respectfully submitted,



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APPENDIX A
VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Once Amended) A method of manufacturing IgG4 immune globulin that comprises the steps of:

(a) adjusting plasma to a pH of about 6.5 and a conductivity of between 3.5 to 6 millisiemens;

(b) contacting the plasma obtained from step (a) with an anion exchange resin to obtain an anion exchange effluent; and

(c) contacting the effluent of step (b) with a cation exchange resin to obtain a cation exchange effluent that comprises IgG4 essentially free of other IgG subtypes.

[concentrating a raw immune globulin solution; freezing the concentrated immune globulin solution; thawing the frozen concentrated immune globulin solution; adding sufficient mono or disaccharide to the thawed concentrated immune globulin solution to yield a solution of about 0.25 to about 0.35 osmolar; filtering the thawed concentrated immune globulin solution; and lyophilizing the concentrated immune globulin solution.]

2. (Canceled) The method of Claim 1, wherein the step of concentrating the raw immune globulin solution comprises concentrating the solution by ultrafiltration.

3. (Canceled) The method of Claim 1, further comprising, prior to said step of concentrating a raw immune globulin solution, the steps of: fractionating a sterilized, purified donor plasma pool to provide a raw immune globulin solution; and adding sodium chloride to the raw immune globulin solution to a final molarity in the range of about 0.03 to 0.05M.

4. (Canceled) The method of Claim 3, further comprising, prior to said step of fractionating a sterilized, purified donor plasma pool, the steps of: providing a sterilized donor blood plasma pool; purifying the donor blood plasma pool; adjusting the pH of the purified donor plasma pool to about 6.5; and adjusting the conductivity of the purified donor plasma pool to a range of about 3.5 to 6.0 millisiemens.

5. (New) The method of claim 1, wherein said plasma is plasma obtained from an immune donor.

6. (New) The method of claim 1, wherein said anion exchange resin is a DEAE Sepharose® resin.

7. (New) The method of claim 1, wherein said cation exchange resin is a CM-Sepharose® resin.

8. (New) The method of claim 1, further comprising the steps of:

(d) adding NaCl to a final concentration of 0.03 to 0.05 M NaCl;

(e) filtering the solution of step (d);

(f) centrifuging the filtrate of step (e);

(g) freezing the supernatant of step (f);

(h) thawing the frozen supernatant of step (g);

(i) adding a monosaccharide or disaccharide to the thawed supernatant of step (h) to a final osmolarity of between 0.22 to 0.35 OsM;

(j) filtering the solution of step (i);

(k) freezing the filtered solution of step (j);

(l) thawing the frozen solution of step (k); and

(m) lyophilizing the solution of step (l).

9. (New) The method of claim 8, wherein said monosaccharide is lactose.

10. (New) A method of treating a patient envenomated by the sting of an insect sting comprising:

administering a composition comprising IgG4 essentially free of other IgG subtypes to a patient envenomated by an insect sting.

11. (New) The method of claim 10, wherein said insect is selected from the group consisting of: flying insects, bees, honey bees, killer bees, wasps, hornets, yellow jackets, and the hymenoptera.

12. (New) The method of claim 10, wherein said composition is prepared using a purification method comprising the steps of:

(a) adjusting plasma to a pH of about 6.5 and a conductivity of between 3.5 to 6 millisiemens;

(b) contacting the plasma obtained from step (a) with an anion exchange resin to obtain an anion exchange effluent; and

(c) contacting the effluent of step (b) with a cation exchange resin to obtain a cation exchange effluent that comprises IgG4 essentially free of other IgG subtypes.

13. (New) A pharmaceutical composition, said pharmaceutical composition comprising IgG4 essentially free of other IgG subtypes and a monosaccharide or a disaccharide.

APPENDIX B

PENDING CLAIMS SUBJECT TO EXAMINATION

1. (Once Amended) A method of manufacturing IgG4 immune globulin that comprises the steps of:

(a) adjusting plasma to a pH of about 6.5 and a conductivity of between 3.5 to 6 millisiemens;

(b) contacting the plasma obtained from step (a) with an anion exchange resin to obtain an anion exchange effluent; and

(c) contacting the effluent of step (b) with a cation exchange resin to obtain a cation exchange effluent that comprises IgG4 essentially free of other IgG subtypes.

5. (New) The method of claim 1, wherein said plasma is plasma obtained from an immune donor.

6. (New) The method of claim 1, wherein said anion exchange resin is a DEAE Sepharose® resin.

7. (New) The method of claim 1, wherein said cation exchange resin is a CM-Sepharose® resin.

8. (New) The method of claim 1, further comprising the steps of:

(d) adding NaCl to a final concentration of 0.03 to 0.05 M NaCl;

(e) filtering the solution of step (d);

(f) centrifuging the filtrate of step (e);

(g) freezing the supernatant of step (f);

(h) thawing the frozen supernatant of step (g);

(i) adding a monosaccharide or disaccharide to the thawed supernatant of step (h) to a final osmolarity of between 0.22 to 0.35 OsM;

(j) filtering the solution of step (i);

(k) freezing the filtered solution of step (j);

(l) thawing the frozen solution of step (k); and

(m) lyophilizing the solution of step (l).

9. (New) The method of claim 8, wherein said monosaccharide is lactose.

10. (New) A method of treating a patient envenomated by the sting of an insect sting comprising:

administering a composition comprising IgG4 essentially free of other IgG subtypes to a patient envenomated by an insect sting.

11. (New) The method of claim 10, wherein said insect is selected from the group consisting of: flying insects, bees, honey bees, killer bees, wasps, hornets, yellow jackets, and the hymenoptera.

12. (New) The method of claim 10, wherein said composition is prepared using a purification method comprising the steps of:

(a) adjusting plasma to a pH of about 6.5 and a conductivity of between 3.5 to 6 millisiemens;

(b) contacting the plasma obtained from step (a) with an anion exchange resin to obtain an anion exchange effluent; and

(c) contacting the effluent of step (b) with a cation exchange resin to obtain a cation exchange effluent that comprises IgG4 essentially free of other IgG subtypes.

13. (New) A pharmaceutical composition, said pharmaceutical composition comprising IgG4 essentially free of other IgG subtypes and a monosaccharide or a disaccharide.